Human Health Effects from Polyfluoroalkyl Chemicals (PFCs)

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SUMMARY

Perfluoroalkyl acids (PFAAs) are a subgroup of polyfluoroalkyl chemicals (PFCs) that industry has produced since the 1950s for their properties of oil and water resistance. Due to the large production of these chemicals and their persistence, exposure in the US population is nearly ubiquitous. The persistence of these chemicals make it a necessity that we better understand them to ensure protection of human and environmental health.

Within the developmental studies that have been completed there are uncertainties and at times conflicting results. Studies have used slightly different indicators, gotten different results for the same indicator, and were unsure whether only PFOA or PFOS and PFOA together cause negative outcomes. This evidence shows that more epidemiologic studies need to be completed to determine exactly what the health effects are for infants exposed in utero, but the studies show the possibility of negative outcomes in humans and encourage the use of caution when dealing with these chemicals.

Studies on the alteration of lipid levels, specifically cholesterol levels, show PFCs are associated with negative heart and health outcomes. These associations are especially alarming because studies show PFCs are not only associated with total cholesterol, but with increasing bad cholesterol leading to cardiovascular disease and atherosclerosis (Costa et al., 2014, Gordon et al. 1989). Heart disease is currently the number one killer in America (Murphy et al., 2013) and can be costly to treat. It is also concerning that we are seeing these results in children 18 and younger indicating that the diseases have the potential for earlier onset creating more years of life living with the disability and more life years lost.

Studies looking into immune related outcomes have different ways of collecting and analyzing their data. Okada et al. has an interesting outcome and it may be beneficial to see if the decreased IgE levels have any impact on allergic or asthmatic outcomes in the child's future. The study by Dong et al. corresponds with previous animal studies finding an increase in immunotoxic effects and PFC levels. The increase in IgE with PFOS and PFOA levels only in children that have asthma is also noteworthy and indicates PFCs may play a role in the causal pathway of asthma. The study by Granum et al. also chose age 3 to determine health outcomes, and they were also able to demonstrate negative health outcomes with elevated PFC concentrations. Overall the immune altering effects of PFCs need more research to be completed

in order to better understand the associations.

PFC exposure has long been known to cause cancer in rodent models, although the evidence in humans has not been as strong. Together, studies show the association of PFOA with kidney, testicular, and breast cancer and also PFOS with breast cancer. These studies show an association across three different groups: workers exposed in an occupational setting, those living in an area known to have high levels in the water supply, and a group that has been known to have a large burden of overall persistent organic pollutants. Cancer can often be a sensitive endpoint and together these studies show that there is an association between PFC exposure and cancer. Further studies are needed to determine other possible associated cancers.

Through these studies we have seen that PFCs are associated with various developmental outcomes including decreased weight, length, and size of infants. Some states have already chosen to set acceptable and safe levels for drinking, ground water, and soil; after seeing all of the potential health impacts from PFCs more states may follow the same

INTRODUCTION

Perfluoroalkyl acids (PFAAs) are a subgroup of polyfluoroalkyl chemicals (PFCs) that industry has produced since the 1950s for their properties of oil and water resistance. They can be found in a variety of products including carpets, furniture, food packaging, and nonstick cookware. PFAAs consist of a fluorinated carbon backbone of varying lengths with a functional group attached to the end (ASTDR, 2009). Two main groups of PFAAs are perfluoroalkyl sulfonates and perfluoroalkyl carboxylates; they are differentiated by containing either a sulfony or carboxyl functional group (Nelson et al. 2010). The strong carbon fluorine bonds cause the molecules to resist degradation and persist in the environment. Due to the large production of these chemicals and their persistence, exposure in the US population is nearly ubiquitous. The main source of exposure to PFCs is currently unclear, but it is suspected that humans can be exposed to PFAAs through products that contain them, food in packaging containing PFAAs, household dust, and drinking water (reviewed in Lau et al., 2007).

Perfluorooctanyl sulfonate (PFOS) and perluorooctanoic acid (PFOA) each consist of an eight carbon backbone attached to a sulfonyl or carboxyl group, respectively. They are two of the most highly produced PFAAs, making them the most commonly found in humans (Kato et al., 2011). Due to their chemical nature they do not accumulate in fat, like many other persistent organic pollutants, but bind to serum albumin and are stored in the serum, liver, and kidneys (Costa et al., 2009). Their chemical structure does not allow the body to degrade the substance, only eliminate it, leading to a long half-life. The mean serum half lives in humans are estimated to be 5.4 years for PFOS and 3.8 years for PFOA (Olsen et al., 2007). Between 1999 and 2008 PFOS, PFOA, perfluorononanoic acid (PFNA) and perfluorohexane sulfonic acid (PFHxS) were found in the serum of over 95% of Americans through the National Health and Nutrition Examination Survey (NHANES) (Kato et al., 2011).

Additionally, children may be at a higher risk for exposure to PFCs, as they spend more time laying and playing on the floor with carpets potentially treated with PFC containing products and where dust containing PFCs accumulates. Children also drink more water and eat more food per unit weight, increasing the amount of chemicals consumed. Studies have shown that PFC concentrations increase during the first few months of life and children ages 3 to 11 have higher PFC concentrations than other age groups (Fromme et al., 2010).

In 2000, the major manufacturer of PFOS and PFOA began to phase these chemicals out. By 2002 PFOS and other perfluoroalkyl sulfonate chemicals were phased out, while PFOA was phased out in 2008. PFOA is still produced by other domestic chemical companies, but to decrease the amount of the chemical entering the environment the EPA started a PFOA stewardship program with the eight major PFOA producers. The stewardship program aims to decrease production of PFOA, PFNA, and other perfluoroalkyl carboxylates by 95% by 2010 and to completely eliminate them by 2015 (EPA). To date,the program has reduced the amount of chemicals produced and released into the environment, but due to their resistance to degradation PFCs continue to persist.

The effort to release fewer PFCs has had an impact on serum levels in the general population. Since discontinuing production of PFOS there has been a significant downward trend in serum levels of Americans. This observation took place between 1999 and 2008 through NHANES; more data continues to be collected and analyses need to be done to determine if the decrease continues. During the same time 1998 to 2008 timeframe PFOA decreased from the initial levels, but stayed relatively the same between 2003 and 2008. PFHxS showed a decrease between 1999 and 2006, but began to increase again after 2006. While PFNA has shown a significant increase in serum levels throughout the 1999 to 2008 timeframe (Kato et al., 2011). The concentrations of these chemicals in the population are in flux during their phase out period, but continue to persist at detectible levels in the body.

While currently no regulation force companies to comply with the PFOA stewardship program, companies have willingly agreed to phase them out. Seeing significant decreases in levels of PFCs in serum reinforces the importance and impact of this program. Unfortunately the stewardship is only domestic and PFAAs continue to be produced overseas in places that often have more lenient rules on their use and disposal. The persistence of these chemicals and the production in other parts of the world make it a necessity that we better understand them to ensure protection of human and environmental health.

METHODS

The sources for this literature review were obtained between June 9, 2014 and July 10, 2014 through Google Scholar. Searches were completed for three PFCs; PFOS, PFOA, and

PFNA. Additional sources were found by looking through the sources of existing papers.

HEALTH EFFECTS

One of the major concerns with the ability to detect PFCs in the serum of nearly all Americans is the potential for negative health effects, especially because these chemicals bioaccumulate and remain in the body for years. Both animal and human studies have shown PFC's such as PFOS and PFOA have negative health effects including developmental, altered lipid metabolism, altered immune responses, and cancer.

DEVELOPMENTAL OUTCOMES

Developmental effects from PFCs are especially concerning considering the vulnerability of children and the potential for lifelong impacts. Negative developmental outcomes in rats and mice include decreased neonatal survival and gestational length, reduced birth and fetal weight, and delayed development and postnatal growth (Fuentes et al. 2006; Gratsy et al. 2003; Butenhoff et al. 2004; Lau et al. 2004, 2006). Many of the health effects seen in animals are at doses considerably higher than average exposures, but based on different excretion rates and half-lives between species and sexes it is important to determine if developmental health effects are seen in humans.

In 2007 Apelberg et al. completed a cross sectional study of births in a Baltimore hospital. They collected cord serum from 293 participants, analyzed them for PFOS and PFOA, and compared them with maternal characteristics and measurements of the infants at birth. After controlling for smoking status, age, race, prepregnancy BMI, previous preterm birth, diabetes, hypertension, weight gain during pregnancy, height, parity, and infant sex they determined that both PFOS and PFOA were negatively associated with birth weight [per ln unit: β= -104g, 95% confidence interval (CI), -213 to 5 for PFOA; per ln unit: β= -69g, 95% CI, -145 to 10 for PFOS], ponderal index, a measure of body mass at birth, (per ln unit: β = -0.070 g/cm^3 * 100, 95% CI, -0.138 to -0.001 for PFOA; per ln unit: β = -0.074 g/cm^3 * 100, 95% CI, -0.123 to -0.025 for PFOS), and head circumference (per ln unit: β = -0.41cm, 95% CI, -0.76 to -0.07 for PFOA; per ln unit: β = -0.32cm, 95% CI, -0.56 to -0.07 for PFOS). No association was found between PFOS or PFOA on gestational age or newborn length.

Also In 2007, Fei et al. published a paper on PFCs and fetal outcomes in the Danish

National Birth Cohort. Their study looked at 1,400 participants with maternal blood samples from gestational weeks 4 to 14 and phone interviews on indicators such as birth weight, duration of pregnancy, and small for gestational age (SGA) infants. After adjusting for gestational age, infant sex, maternal age, socio-occupational status, parity, prepregnancy BMI, and gestational week at blood draw they determined that PFOA levels were inversely associated with birth weight ($\beta = -10.63$ g; 95% CI, −20.79 to −0.47) and neither PFOS nor PFOA maternal levels were consistently associated with risk for preterm birth or low birth weight. In addition, there was no association between maternal PFOS or PFOA levels and SGA infants.

In 2008 Fei et al. published an additional paper on the same cohort, but used the indicators of ponderal index, placental weight, birth length, and head and abdominal circumference measured by either a nurse or trained midwife. They found maternal PFOA levels were inversely associated with birth length (per ng/ml increase β= -0.069 cm, 95% CI, 0.024 to 0.113) and abdominal circumference (per ng/ml increase β= 0.059 cm, 95% CI 0.012 to 0.106). Maternal PFOS was not associated with any of the indicators; PFOA also had slight negative associations with placental weight and head circumference and a slight positive association with ponderal index, but none of these associations were significant.

The 2007 study by Fei et al. finds only PFOA has an inverse relationship with birth weight and that PFOS is not associated with any of the birth characteristics, whereas the study by Apelberg et al. finds a negative association between both PFOA and PFOS with birth weight, ponderal index, and head circumference. The 2008 study by Fei again found PFOS did not have an association with the indicators, but PFOA had a significant inverse relationship with birth length and abdominal circumference and a slight negative association with placental weight and head circumference. These results agree with Apelberg for head circumference but differ by finding a relationship with birth length; abdominal circumference and placental weight were not tested by Apelberg. In addition Apelberg found a negative association with ponderal index between PFOA and PFOS while Fei found a slight positive correlation with PFOA. These studies chose similar or the same indicators and slightly different methods to analyze and determine that PFOA and PFOS exposure negatively impact birth weight, ponderal index, and head circumference and PFOA may impact birth length and abdominal circumference.

Indicator	Apelberg		Fei 2007		Fei 2008	
	PFOS	**PFOA**	**PFOS**	**PFOA**	**PFOS**	**PFOA**
Birth Weight	-*	-*	null	-*		
Birth Length	null	null			null	-*
Ponderal Index	-*	-*			null	+
Head Circumf.	-*	-*			null	-
Abdom Circumf.					null	-*
Gestational Age	null	null	null	null		
Placental Weight					null	-

Table indicating the direction of the relationship (- or +) between PFOA and PFOS exposure with fetal indicators from Apelberg et al. 2007, Fei et al. 2007, and Fei et al. 2008. * indicates significance.

These studies used similar indicators, but utilized different methods. Fei et al. used maternal serum from early in pregnancy while Apelberg used cord blood. Cord blood may be more representative of the total exposure to the neonate rather than a single blood draw early in pregnancy. Fei et al. had a larger nationwide sample, rather than a sample from a single hospital, making it more representative and possibly decreasing selection bias. In the 2007 study Fei chose to use self-reporting, which has the potential to introduce recall bias and could influence the results. It is interesting that Apelberg did not include socioeconomic status (SES) as a confounder, but he addresses this stating that it did not alter the outcome of the model. The papers have slightly different methods and outcomes, but they both indicate an association between PFCs and negative developmental outcomes at typical exposure levels.

The previous studies on developmental outcomes came from samples at average levels of exposure, but another study by Nolan et al. in 2009 looked at effects in a highly exposed population. They examined health outcomes for residents that received water from the Little Hocking Water Association (LHWA) in Washington County, Ohio. Residents in this area have been known to have serum PFOA levels 80 times higher than the rest of the US population (Emmet et al., 2006). They researchers created three categories: those who received all of their

water from LHWA, those who received water from LHWA in addition to other facilities, and those that received no water from LHWA. There were 1,446 eligible infants born within these 3 categories. After correcting for maternal age, gestational age, sex, race, and population level SES the authors determined the incidence of low birth weight, preterm birth, mean birth weight and mean gestational age did not significantly differ by water category. This study is important because it looks at a group of women and infants with high PFOA concentrations in their drinking water but does not detect a difference in outcomes, where the previous studies detected significant differences with much lower PFOA levels. This study utilized census data and medical records, so it was unable to account for individual factors such as the use of at home water filters or bottled water, introducing the opportunity for confounding.

Within the developmental studies that have been completed there are uncertainties and at times conflicting results. Studies used slightly different indicators, got different results for the same indicator, and were unsure whether only PFOA or PFOS and PFOA together cause negative outcomes. This evidence shows that more epidemiologic studies need to be completed to determine exactly what the health effects are for infants exposed in utero, but the studies above certainly show the possibility of negative outcomes in humans and encourage the use of caution when dealing with these chemicals.

ALTERED LIPID OUTCOMES

In addition to developmental effects a health effect commonly associated with exposure to PFCs is an alteration of lipid levels. Although, effects differ in humans and animals. Hypolipidemia, or low cholesterol, was seen in animals given high doses of PFCs (Seacat et al. 2002) while in humans the opposite effect, hyperlipidemia, has been shown (C8 Science Panel 2008). The reason for the difference between the effects in humans and animals is not yet known, but in both species lipid levels are altered to unhealthy levels creating different negative health effects.

Previously there had been conflicting results about altered lipid metabolism in occupational cohort studies, including studies on the same cohort (Ubel et al. 1980, Gilliland et al. 1996). A more recent cohort study by Costa et al. in 2009 examined 30 years of medical surveillance from 53 men that either previously or currently worked in a PFOA plant. They analyzed the most recent data from the cohort, collected between April 2000 and May 2007. This

included physicals and blood draws from the participants. After analyzing the data and correcting for age, years of exposure, year of PFOA sampling, BMI, smoking, and alcohol consumption they determined there was a significant association between PFOA serum levels and total cholesterol and uric acid. Comparing exposed workers to unexposed workers the average uric acid was increased by 0.5 mg/dL (95% CI, 0.06 to 0.94) and total cholesterol was increased by 21.7 mg/dL (95% CI, 6.83 to 36.6). This study reinforces that there is an association between PFOA exposure and an alteration in lipid metabolism. It also spurs interest into whether or not PFOS can act in a similar manner and alter cholesterol levels.

A cross sectional study by Nelson et al. in 2010 examined physical exam data, blood draws and questionnaires from the 2003-2004 NHANES. They wanted to look further into the relationship between serum PFC levels and lipid and weight regulation. They examined the association between serum PFOS, PFHxS, PFOA, and PFNA and cholesterol, body size (BMI and waist circumference), and insulin resistance. After controlling for age, sex, race/ethnicity, SES, saturated fat intake, exercise, time in front of a TV/ computer, alcohol consumption, smoking, and for women, parity, they determined there is a positive association between total and non-high-density ("bad") cholesterol and concentrations of PFOS, PFOA, and PFNA. Those in the highest quartile of PFOS levels had total cholesterol levels 13.4 mg/dL (95% CI, 3.8-23.0) higher than those in the lowest quartile. PFOA had an effect estimate of 9.8 mg/dL (95% CI -0.2 to 19.7) and PFNA had an effect of 13.9mg/dL (95% CI, 1.9 to 25.9). PFHxS showed the opposite effect and there was no association between any of the PFCs and body size or insulin resistance. This study shows that not only PFOA, but PFOS and PFNA, can significantly alter cholesterol levels and may be acting to increase overall cholesterol levels by increasing "bad" cholesterol.

Together these studies show the impact of PFCs and lipid metabolism in adults. The study by Costa et al. contains valuable information because of the long duration the cohort has been observed, but it has a much smaller sample size. In Costa et al. the authors were looking at a wide array of outcomes while completing the study, including glucose, proteins, and blood cells; but, when they found an association between lipid levels and uric acid, more in-depth analyses were done by adding additional exclusion criteria and possible related confounders. They narrowed in on the information by including necessary and relevant items related to cholesterol and lipid metabolism into their model. The study by Nelson is a cross-sectional

study, but it has a large and representative sample. This study also looked at the outcome of body size and PFC level, so there are more things the authors controlled for in their sample including parity, exercise, and time in front of a TV/computer that the previous study did not control for. It is interesting that PFHxS has the opposite effect from the other PFCs, and will be interesting to determine in the future how it interacts with the body differently. These studies together show the negative effects exposure to PFCs can have on normal lipid metabolism in both occupationally exposed workers and those at typical exposure levels.

Previously, there was only research on adults; but as mentioned earlier, children often have higher PFC serum burdens. In 2014 Geiger et al. looked at dyslipidemia, abnormal lipid levels, in children and adolescents between 12 and 18 years old. This cross-sectional study had 815 participants from the 1999 to the 2008 NHANES. After controlling for age, race/ethnicity, annual household income, physical activity, and serum cotinine they determined that serum PFOS and PFOA were associated with high total cholesterol, and high low-density lipoprotein (LDL) cholesterol. Comparing the third tertile to the first, the referent group, the multivariate odds ratio (OR) for high total cholesterol is 7.0 (95% CI, 1.4 to 12.6) for PFOA and 5.9 (95% CI, 0.1 to 11.6) for PFOS. The ORs for LDL cholesterol are 8.2 (95% CI, 3.0 to 13.3) for PFOA and 7.0 (95% CI, 2.0 to 12.0) for PFOS. Neither PFOS nor PFOA were associated with high-density lipoprotein levels or triglycerides. This study shows that the association we see in adults with regard to serum PFC levels in alteration in normal cholesterol levels is occurring in children as well.

The information from these three studies is valuable because alteration in lipid levels, specifically cholesterol levels, is associated with negative heart and health outcomes. These associations are especially alarming because Costa et al. and Geiger et al. show PFCs are not only associated with total cholesterol, but with increasing bad cholesterol leading to cardiovascular disease and atherosclerosis (Costa et al., 2014, Gordon et al. 1989). Heart disease is currently the number one killer in America (Murphy et al., 2013) and can be expensive to treat. It is also concerning that we are seeing these results in children 18 and younger indicating that the diseases have the potential for earlier onset making more (decreasing quality of life) years of life living with the disability and more life years lost.

ALTERED IMMUNE OUTCOMES

Immunotoxicity is another health effect that has been noted in both animal and human studies with exposure to PFCs. Animal studies have suggested that PFOA may alter the immunoglobulin E (IgE) response to environmental allergens by increasing serum levels and enhancing hypersensitivity response to ovalbumin (Fairly et al., 2007). IgE is an antibody produced by the body in response to a perceived threat and is involved in allergic reactions. In another study on allergic response, PFOS exposure in mice decreased baseline airway resistance but increased airway responsiveness (Loewen et al. 2011). The category of immunotoxicity covers a wide array of topics, but some of the main associations seen in humans are with PFC exposure and asthma, allergies and decreased levels of vaccine antibodies. Also seen with immunotoxiciy, the effects of PFCs differ between humans and animals as well as by sex.

A study by Okada et al. in 2012 followed a cohort from 2002 to 2005 in Sapporo Japan to determine if PFOS or PFOA exposure was linked to IgE levels and asthma/ allergic diseases. They collected surveys and a blood sample from the mother before delivery, medical records and cord blood samples from birth, and another survey when the child was 18 months including questions on infant allergies and infections. They then analyzed the mother's serum for PFOS and PFOA levels and the cord blood for IgE levels. After controlling for maternal age, maternal allergic history, parity, infant gender, birth season, distance from home to highway, and blood sampling period they stratified by gender to determine cord blood IgE levels had a significant inverse relationship with maternal PFOA concentrations, but only in females (adjusted β= -1.43IU/mL 95% CI, -2.15 to -0.42). Maternal PFOS and PFOA levels were not significantly associated with food allergy, eczema, wheezing, or otitis media at age 18 months.

In a study by Dong et al. in 2013 they conducted a case control study in northern Taiwan to determine if serum PFC levels are associated with immunologic effects including asthma. They recruited 231 asthmatic children and 225 nonasthmatic controls. Through a face-to-face interview and blood draw they were able to obtain information on allergies, asthma, and PFC serum levels. After controlling for age, sex, parental education, BMI, environmental tobacco smoke (ETS), and month of survey they determined that comparing children from the fourth quartile of exposure to the first there was 2.63 (95% CI, 1.48 to 4.69) times the odds of having asthma for PFOS, 4.05 (95% CI, 2.21 to 7.42) time the odds for PFOA, 3.83 (95% CI, 2.11 to 6.93) times the odds for PFHxS, and 2.56 (95% CI, 1.41 to 4.6) times to odds for PFNA. Also, the serum IgE levels were not associated with any of the PFCs in children without asthma, but in

children with asthma PFOS and PFOA were both associated with increased IgE levels.

A study by Granum et al. in 2013 examined a sub-cohort of the Norwegian Mother and Child Cohort Study to determine if in prenatal exposure to PFCs had any effect on vaccine or immune-related health outcomes in children up to 3 years of age. There were 3 annual questionnaires, blood samples taken from the mothers at the time of delivery, and blood samples from the children at age 3. Confounders considered for the final model consisted of APGAR score after 1 minute, passive smoking for the child, child's age when starting day care, breast feeding, maternal asthma, maternal BMI, maternal age, maternal passive smoking, and maternal smoking. They were able to determine that there is an inverse relationship between the level of anti-rubella antibodies in the child's serum at 3 years and PFC levels (β=-0.40 95% CI, -0.64 to -0.17) for PFOA, (β= -1.38 95% -2.35 to -0.40) for PFNA, (β= -0.38 95% CI, -0.66 to -0.11) for PFHxS, and (β= -0.08 95% CI, -0.14 to -0.02) for PFOS. There was also a positive association between maternal PFOA and PFNA and the number of common colds the child had and between maternal PFHxS and episodes of gastroenteritis. No significant associations were found between PFC concentration and allergy or asthma related outcomes investigated.

All three of these studies looked at slightly different immune related outcomes and had different ways of collecting and analyzing the data. The studies by Okada et al. and Dong et al. both used IgE levels, but in Okada samples were taken from cord blood and there was an association between increased PFOA and decreased IgE in females at birth, while in Dong serum samples were taken from the children at 3 years of age and there was and there was an association between PFOS and PFOA with IgE levels in children with asthma. Okada et al. has an interesting outcome and it may be beneficial to see if the decreased IgE levels have any impact on allergic or asthmatic outcomes in the child's future. The study by Dong et al. corresponds wtih previous animal studies finding an increase in immunotoxic effects and PFC levels. The increase in IgE with PFOS and PFOA levels only in children that have asthma is also noteworthy and indicates PFCs may play a role in the causal pathway of asthma. The study by Granum et al. also chose age 3 to determine health outcomes, and they were also able to demonstrate negative health outcomes with elevated PFC concentrations. Overall the immune altering effects of PFCs need more research to be completed in order to better understand the associations.

CANCER OUTCOMES

An additional health outcome associated with PFC exposure is cancer. Cancer is a common outcome in rat studies; PFOA is known to induce tumors in the liver, testes and pancreas (Biegel et al. 2001). While in monkeys exposed to PFOA for 26 weeks there was no incidence of cancer after exposure (Butenhoff et al. 2002). During a two year study of rats there was a significant increase in mammary fibroadenomas and Leydig cell adenomas, suggesting PFOA may also lead to breast cancer (Sibinski et al. 1987). There is a wide array of types of cancer and the species cancer occurs after exposure to PFCs. Due to the long half-life of the chemicals it is important to determine cancer outcomes in humans.

A good place to start examining cancer outcomes, often having a long latency period, in humans are occupational cohorts due to the high exposures and long exposures durations. In 2012 Steenland and Woskie analyzed data from an occupational cohort of 5,791 workers that ran from 1979 to 2004. From the PFOA levels in 1,308 workers they were able to create a job exposure matrix. They then used this to compare the estimated average PFOA levels from the cohort to 2 referent groups, other DuPont workers and the US population. They used the comparison to other DuPont workers to try and eliminate the influence of the healthy worker effect. From these analyses they were able to determine that PFOA exposed employees had a significant increase in mesothelioma (SMR = 2.85, 95% CI 1.05 to 6.20), chronic renal disease (SMR = 3.11, 95% CI 1.66 to 5.32) and there was an increase in kidney cancer deaths with increasing PFOA levels; SMRs (95% CIs) by increasing exposure quartile were 1.07 (95% CI: 0.02, 3.62), 1.37 (95% CI: 0.28, 3.99), 0 (95% CI: 0, 1.42), and 2.66 (95% CI: 1.15, 5.24) (trend test $p = 0.02$). They state in the study that the increase in mesothelioma is likely due to exposure to asbestos. They also state that many cancers such as testicular and breast cancer did not have enough cases to be analyzed. This new information on renal disease and kidney cancer is important for understanding how PFOA acts in humans. Additional studies should to be done on this cohort to determine any new cases of cancer or causes of mortality.

A recent 2013 study by Barry et al. looked at cancer incidence in 32,254 residents of the Mid-Ohio valley where there are elevated levels of PFOA in the drinking water due to chemical plant emissions. They utilized the cohort method and collected blood samples between 2005 and 2006 to get a baseline serum level. They then calculated retrospective yearly PFOA concentrations during the period of 1952 and 2011. Between 2008 and 2011 they collected

additional data on medical history through interviews that were validated through medical records and cancer registries. After adjusting for time-varying smoking, time-varying alcohol consumption, sex, education, and stratifying by 5 year period of birth year they determined there was a positive association between PFOA level and kidney [hazard ratio (HR) = 1.10, 95% CI 0.98 to 1.24] and testicular cancers (HR = 1.34, 95% CI 1.00 to 1.79). This study was completed on a much larger population and was also able to determine an association between PFOA exposure and kidney cancer. It is also interesting that in this larger cohort of highly exposed individuals they were able to determine an association with PFOA and testicular cancer, where the previous study did not have enough cases to analyze.

In 2011 Bonefeld et al. completed a case control study on breast cancer with 31 cases and 115 controls from various Greenlandic districts. The samples were collected between 2000 and 2003, then analyzed for PFCs and other persistent organic pollutants. After adjusting for age, BMI, pregnancy and cotinine they determined there was a significant association between both PFOS and PFOA and breast cancer. The cases had a mean PFOS concentration of 45.6 ng/ml (95% CI 45.7 to 69.3) compared to controls with 21.9ng/ml (95% CI 31.1 to 46.0) giving a p value < 0.0001. For PFOA, cases had an average of 2.5ng/ml (95% CI 2.2 to 3.4) and controls had an average of 1.6ng/ml (95% CI 2.11 to 2.9) giving a p value of 0.04. This study was able to detect a correlation between PFCs and breast cancer, where the study by Steenland and Woskie was unable, due to lack of data. This is also important because of the links seen between PFCs and breast cancer in animal models. This was a case control study and there may be other confounders in this relationship but it is important to know that both PFOS and PFOA exposure may be a risk factor for breast cancer.

PFC exposure has long been known to cause cancer in rodent models, although the evidence in humans has not been as strong. Together these three studies show the association of PFOA with kidney, testicular, and breast cancer and also PFOS with breast cancer. These studies also show an association between three different groups: workers exposed in an occupational setting, those living in an area known to have high levels in the water supply, and a group that has been known to have a large burden of overall persistent organic pollutants. There is also study diversity between the three having two cohort and one cross sectional study. Cancer can often be a sensitive endpoint and together these studies show that there is an association between PFC exposure and cancer. Further studies are needed to determine other

possible associated cancers.

EPA/STATE POSITIONS

Several states have had their own individual issues with PFCs and have generated their own response to the problem. A summary of developed action levels, screening levels, provisional health advisories for various media are tabulated below.

Alabama had an incident where PFCs were discharged from a plant into the water source and were then found in biosolids that had been spread on fields as fertilizer. From this, EPA Region 4 generated a residential soil screening levels for PFOS and PFOA of 6mg/kg for PFOS and 16mg/kg for PFOA. In addition, provisional health advisories for PFOS and PFOA were generated; 0.2µg/L for PFOS and 0.4µg/L for PFOA. After testing samples of biosolids and soils that had received the biosolids, none of them were over the soil screening levels. Also, none of the samples from public drinking water sources were above the provisional health advisories, but three private drinking water wells were (EPA Region 4 Water Protection).

California has chosen to include PFCs on their list of chemicals of concern, but they have not conducted any risk assessment on the chemicals.

Minnesota has also had a PFC issue due to the 3M production plants in their state. They have had high PFC levels around the production plants, disposal facilities, and water sources located close by. In 2009 they generated a Chronic Non-Cancer Health Risk Limit for drinking water for PFOS and PFOA of 0.3µg/L. In addition Minnesota set regulations on the amount of fish that should be consumed from bodies of water with elevated PFC levels. If the PFOA levels in the fish tissue are greater than 40ng/g, fish caught from that area should only be eaten one meal a week, but if the levels are over 200ng/g it is only safe to have one meal per month (Oliaei et al., 2013). Minnesota and Region 5 EPA are currently working on a project to determine the amount of PFCs that enter crops when grown on soil containing the chemicals.

The state of New Jersey also has PFC producing factories, and because of them there has been a concern about the chemicals entering drinking water sources. The state generated a lifetime Drinking Water Screening Level for PFOA of 0.04µg/L. This is an order of magnitude lower than levels from other states, but it is intended to be protective over a lifetime. New Jersey also created a Ground Water Criterion for PFNA of 0.02µg/L.

Category/ PFC	Alabama/ EPA Region 4	EPA HQ	Minnesota	New Jersey	West Virginia
Action Level (Short term exposure)					
PFOS	---	---	---	---	---
PFOA	---	---	---	---	0.5µg/L (Drinking water)
Screening Level	**Short term exposure**		**Lifetime exposure**		
PFOS	6mg/kg (soil)	---	---	---	---
PFOA	16mg/kg (soil)	---	---	0.04µg/L (drinking water)	---
Provisional Health Advisory (Short term Exposure)					
PFOS	---	0.2µg/L (drinking water)	---	---	---
PFOA	---	0.4µg/L (drinking water)	---	---	---
Health Risk Limit (Chronic noncancer)					
PFOS	---	---	0.3µg/L(drinking water)	---	---
PFOA	---	---	0.3µg/L (drinking water)	---	---
Fish consumption					
PFOS	---	---	---	---	---
PFOA	---	---	>40ng/g = 1 meal/week	---	---
	---	---	>200ng = 1 meal/month		
Ground Water Criterion (Lifetime exposure)					
PFNA	---	---	---	0.02µg/L (drinking water)	---

West Virginia and EPA regions 3 and 5 entered into an Administrative order on Consent, which made the action level for PFOA in drinking water 0.5µg/L. in 2005 they changed the

action level to 0.4μg/L.

The state of Washington regularly monitors PFCs in surface water, waste water treatment plants, and Osprey Eggs.

CONCLUSION

Within the past ten years there has been a push for more research to gain a better understanding of how and if PFCs affect humans. Through these studies we have seen that PFCs are associated with various developmental outcomes including decreased weight, length, and size of infants. The results for these studies were not always consistent across the board, but for many of the outcomes more than one study was able to find an association. Altered lipid metabolism is another health outcome found in several studies. Both PFOS and PFOA have been found to increase lipid levels in groups such as occupational workers, average exposed adults, and children. This shows that negative health outcomes from PFC can be far-reaching. In children PFCs have been shown to alter immune responses including a change in typical IgE levels and links to asthma. Cancer is also more recently being seen as a health outcome associated with PFCs. Just now, many years after exposure, there are correlations between exposure and liver and kidney cancer. All of these health outcomes have the potential for significant negative impacts and the use and regulation of PFCs need to be evaluated. Some states have already chosen to set acceptable and safe levels for drinking, ground water, and soil; after seeing all of the potential health impacts from PFCs more states may follow the same footsteps.

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